Remarks

Claims 1-66 are pending. Claims 1-10 have been amended. Claims 65 and 66 has been added. Claims 11-64 have been withdrawn from consideration as being drawn to a non-elected invention.

Summary of Interview

Applicants would like to thank Examiner Pak for her comments during the telephone interview of May 29, 2008, during which the 35 U.S.C. § 102 and 35 U.S.C. § 112 rejections were discussed.

Specifically, Applicants pointed out that the Bishopric et al. reference does not represent evidence that the claimed invention was known or used by another prior to invention (as required under 102(a)) based on the fact that these authors were merely reviewing the work of Drs. Min and Ying-Mei published in the same journal. In fact, Bishopric et al. specifically credits Drs. Min and Ying-Mei for the discovery that "Trx mutants in which only one of the two active cysteine residues is mutated can still associate with ASK1" (Page 1238 first column). As Drs. Min and Ying-Mei are the listed inventors of the instant application, Applicants argued that Bishopric et al. should not be available as prior art under 35 U.S.C. § 102(a). Examiner Pak therefore agreed to withdraw this rejection.

Applicants further discussed a potential amendment in light of Yodoi et al. reference. Specifically, Applicants noted that Yodoi et al. disclosed making Thioredoxin (TRX) variants that are stable under non-reducing conditions that is still able to enhance AP- transcriptional activity. To do this, they made TRX^{C35A} and $TRX^{C32S/C35S}$ mutations. They conclude from these experiments that the Cys resides in the active center of the TRX variant must remain unsubsituted (see abstract). Consequently, while they may have disclosed a TRX variant as claimed, they did not disclose a use for this variant. In contrast, Applicants have disclosed a significant advantage to substituting one, but not both of the Cys residues in the active center of TRX which can be used to prevent apoptosis. Applicants discussed the possibility of amended claims 1 and 7 to recite a composition comprising a mutant TRX (Cys residue at position 32 or

35) and a pharmaceutically acceptable carrier. Examiner Pak agreed that this should overcome the rejection and be unobvious in view of Yodoi et al.

Applicants further discussed amending claims 1 and 7 to recite a structure for mutant thioredoxin based on reference to 90% sequence identity to SEQ ID NO:1 (or SEQ ID NO:2 or 3) while further requiring a Cys residue at position 32 or 35. Examiner Pak agreed that this amendment would overcome the written description and enablement rejections.

Rejection Under 35 U.S.C. § 101

Claims 1-10 were rejected under 35 U.S.C. § 101 as being directed to a non-statutory subject matter. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Office Action posits that the claims do not distinguish over thioredoxins as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. This rejection is moot in light of Applicants' amendment of claims 1 and 7 reciting the mutations of SEQ ID NO:1 and further requiring a pharmaceutically acceptable carrier. Applicants therefore respectfully request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, second paragraph

A. Claims 3-4, 6, and 9 and claims 5-6 and 10 depending therefrom were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Specifically, claims 3 and 9 were rejected for reciting the phrase "the amino acid alteration" without antecedent basis. Claims 3 and 9 have been amended to depend from claim 2, which recites "an amino acid alteration…"

Claims 4 and 6 were rejected for reciting the phrase "the substitution or deletion" without antecedent basis. Claims 4 and 6 have been amended to depend from claim 3, which recites "a cysteine substitution or deletion."

B. Claims 4-6 and 10 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claims 6 and 10 were rejected for reciting the phrase "residue 32 or an analogous residue," "residue 35 or an analogous residue," or "residue 69 or an analogous residue." The Office Action posits that the metes and bounds of the phrases are not clear since Applicants do not recite the reference amino acid sequence for the wild-type thioredoxins. Applicants have therefore amended claim 1 to recite SEQ ID NO:1 as the reference sequence. Applicants respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, first paragraph

A. Claims 1-10 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Office Action posited that recitation of "thioredoxin" fails to provide a sufficient description of the claimed genus of proteins as it allegedly merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. Pursuant to the Telephone Interview with Examiner Pak, Applicants have amended claims 1 and 7 to recite that "the thioredoxin molecule comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, wherein the thioredoxin molecule comprises a cysteine at residue 32 or 35 but not both, wherein the thioredoxin molecule can bind ASK1."

Support for the addition of the phrases "wherein the thioredoxin molecule comprises a cysteine at residue 32 or 35 but not both" and "wherein the thioredoxin molecule can bind ASK1" can be found at least on page 14, lines 23-25.

Support for the addition of the phrase "the thioredoxin molecule comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:1" can be found at least on page 19, lines 7 to 9. Here, reference is made to polypeptides that are about 70, 75, 80, 85, 90, 95, 98,

or 99% homologous to the sequences of SEQ ID NO:2 or SEQ ID NO:3. However, SEQ ID NO:2 and SEQ ID NO:3 are disclosed to be C32S and C35S mutants of SEQ ID NO:1, respectively. While Applicants submit that this provides sufficient support for amendments herein to claims 1 and 7, Applicants have further added new claims 65 and 66 wherein SEQ ID NO:2 is used as the reference sequence to facilitate prosecution.

Applicants therefore respectfully request withdrawal of this rejection.

B. Claims 1-10 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Office action states that "the specification only enables a mutant of the thioredoxin having the amino acid sequence of SEQ ID NO:1, wherein said mutant consists of an amino acid substitution at position 32, 35, and/or 69 of SEQ ID NO:1, wherein said mutant continues to have thioredoxin activity and is resistant to oxidizing effects of cytokines or reactive oxygen species or S-nitrosylation of a SH-group by nitrous oxide." The basis of the rejection is therefore understood to be the recitation of "thioredoxin" without reference to an amino acid sequence. Pursuant to the Telephone Interview with Examiner Pak, Applicants have amended claims 1 and 7 to recite that "the thioredoxin molecule comprises an amino acid sequence having at least 90% sequence identity to SEQ ID NO:1, wherein the thioredoxin molecule comprises a cysteine at residue 32 or 35 but not both, wherein the thioredoxin molecule can bind ASK1."

Applicants disclosed the use of the mutant thioredoxin to inhibit Apoptosis Signal-regulating Kinase 1(ASK1). Applicants further disclosed that the ability of thioredoxin to bind ASK1 is based on residues C32 and C35, but that only one of them is required. Applicants further disclosed that thioredoxin molecule is resistant to the oxidizing effects of cytokines or reactive oxygen species if it lacks one of residues C32 or C35. Applicants further disclosed that thioredoxin molecule is resistant to S-nitrosylation of a SH-group by nitrous oxide if the thioredoxin mutant comprises a deletion, substitution or mutation at C69 (or comparable residue)(page 48, lines 10-12).

As such, the skilled artisan would be able to identify a thioredoxin variant having 90% sequence identity to SEQ ID NO:1 that is able to bind ASK1 and still be 1) resistant to the

oxidizing effects of cytokines or reactive oxygen species or 2) resistant to S-nitrosylation of a SH-group by nitrous oxide without undue experimentation.

Applicants therefore respectfully request withdrawal of this rejection.

Rejection Under 35 U.S.C. § 102

A. Claims 1-10 were rejected under 35 U.S.C. § 102(a) as being anticipated by Bishopric et al. [reference to Warren et al is understood to be a typographical error]. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed in the Telephone Interview with Examiner Pak, the Bishopric et al. reference does not represent evidence that the claimed invention was known or used by another prior to invention (as required under 102(a)) based on the fact that these authors were merely reviewing the work of Drs. Min and Ying-Mei published in the same journal. In fact, Bishopric et al. specifically credits Drs. Min and Ying-Mei for the discovery that "Trx mutants in which only one of the two active cysteine residues is mutated can still associate with ASK1" (Page 1238 first column). As Drs. Min and Ying-Mei are the listed inventors of the instant application, Bishopric et al. is not be available as prior art under 35 U.S.C. § 102(a). Applicants respectfully request the withdrawal this rejection.

B. Claims 1-10 were rejected under 35 U.S.C. § 102(b) as being anticipated by Yodoi et al. (EP 0 853 088 A2). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

As discussed in the Telephone Interview with Examiner Pak, Yodoi et al. disclosed making TRX variants that are stable under non-reducing conditions that are still able to enhance AP-transcriptional activity. To do this, they made TRX^{C35A} and $TRX^{C32S/C35S}$ mutations and concluded from these experiments that the Cys resides in the active center of the TRX variant must remain unsubsituted (see abstract). Consequently, while they may have disclosed a TRX variant as claimed, they did not disclose a use for this variant. In contrast, Applicants have disclosed a significant advantage to substituting one, but not both of the Cys residues in the active center for purposes of preventing apoptosis. Applicants have therefore amended claims 1

and 7 to recite a composition comprising a mutant TRX (Cys residue at position 32 or 35) and a pharmaceutically acceptable carrier. A pharmaceutical composition comprising the claimed TRX mutants was not disclosed in Yodoi et al and is not made obvious by Yodoi et al. since they did not disclose a therapeutic use for the claimed mutants. Applicants respectfully request the withdrawal this rejection.

A Credit Card Payment authorizing payment in the amount of $60.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(1) for a One Month Extension of Time, and a Request for Extension of Time are hereby enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,
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